REMARKS

Status Summary

The examiner acknowledges entry of the response to a requirement for restriction/election of claims, filed September 23, 2002, and has made the election final notwithstanding traversal. Claims 28, 30-31, and 35-36 are therefore withdrawn as being directed to non-elected inventions. Claims 23-27, 29, and 32-34 were examined. The elected species of "cervical cancer" (claim 29) is deemed to be free of the prior art, and thus the next species of "breast cancer" was examined. Official action, page 2.

Claims 27 and 34 are objected to for lack of formalities. Claims 23-26 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claims 23, 25-26, and 32 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to teach one skilled in the art how to make and use the claimed invention. Claims 23-25 and 27 are rejected under 35 U.S.C. § 102(b) as being anticipated by Wojtowicz-Praga et al. (1996) *J Immunol* 19(3):169-175 (Wojtowicz-Praga). Claims 23-27 and 29 are also rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Wojtowicz-Praga in view of Arteaga et al. (1993) *J Clin Invest* 92:2569-2576 (Arteaga) and further in view of PCT International Publication No. WO 94/09815 to Segarini et al. Claims 32-33 are further rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,695,770 to Raychaudhuri et al. in view of Hoefer et al. (1995) *Cancer Immunol Immunother* 41:302-308 or in view of Arteaga.

Claims 23-26 are amended as indicated above. Claims 27, 28, 30-31, and 34-37 are canceled. New claims 38-43 are added. Reconsideration in view of the amendments and following remarks is respectfully requested.

Objections to the Claims

Claim 27 is objected to as being directed to, in part, methods for the treatment of parasitic infections and viral infections, which are non-elected inventions. Claim 34 is objected to as dependent on a previously canceled claim. Official action, page 3. Claims 27 and 34 are canceled and thus the claim objections are rendered moot.

Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 23-26 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Official action, pages 3-4.

Claim 23 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly lacking a clear identification of the condition to be treated. Claim 23 is amended to specify a method for treating cancer or neoplasms.

Claim 24 is rejected under § 112, second paragraph, for lack of antecedent basis for the term "secreted" in claim 23. Claim 24 is amended to delete the word "secreted."

Claim 26 is rejected under § 112, second paragraph, for lack of antecedent basis for the term "TGF antagonist" in claim 25. Claim 26 is amended to refer to a "TGFβ antagonist."

Based on the foregoing amendments, applicants respectfully request that the rejection of claims 23-26 under § 112, second paragraph be withdrawn.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 23, 25-26, and 32 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to teach one skilled in the art how to make and use the claimed invention. The examiner states that while the specification enables methods for the treatment of neoplasms or cancer, including induction of a cytotoxic T lymphocyte response, via administration of (i) an adjuvant which induces a cytotoxic T lymphocyte response and (ii) an antagonist of an immunosuppressive factor, wherein the immunosuppressive factor is TGFβ, it does not enable methods commensurate with the scope of the pending claims. In brief, the examiner suggests that cancer therapies and the use of a TGFβ antagonist are limits to the scope of enabling disclosure. Despite that additional immunosuppressive factors are identified in the specification (*e.g.*, interleukin 10, prostaglandin (PGE2), immunosuppressive acidic protein (IAP), and lipocortin-1 (LC1), the examiner states that the specification only provides examples of TGFβ antagonists and these results are not readily extrapolated to the use of antagonists of any immunosuppressive factor, particularly when antagonists of other immunosuppressive factors are not identified and/or their *in vivo* activities are unknown. Official action, pages 4-7. This rejection is respectfully traversed.

As a matter of Patent Office practice, the burden rests upon the Patent Office to establish a *prima facie* case of a failure to comply with 35 U.S.C. § 112, first paragraph, with respect to the invention described and claimed in applicants' presumptively enabling patent application. *In re Marzocchi*, 58 C.C.P.A. 1069, 439 F.2d 220, 169 USPQ 367 (C.C.P.A. 1971). The legal standard for enablement is whether one reasonably skilled in the art could make and use the invention based on the disclosure of the application and knowledge in the

art without undue experimentation. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

Applicants respond that the examiner has failed to make a *prima facie* case of lack of enablement. Specifically, the examiner makes general allegations as to the unpredictability of the claimed methods but fails to provide any documentation in support thereof. In contrast to the examiner's assertion, applicants respond that one skilled in the art could employ additional antagonists of immunosuppressive factors to perform the claimed invention.

With respect to the examiner's contention that the enabling scope of the disclosure is limited to methods for treatment of cancer or neoplasms, applicants note that claim 23 is amended to specify methods for the treatment of cancer of neoplasms. This amendment is made for the sole purpose of facilitating prosecution.

With respect to the examiner's contention that the disclosed methods are limited to methods that employ a TGFβ antagonist, applicants respond that a skilled artisan could readily select an antagonist of an immunosuppressive factor for preparation of a composition of the invention. The present invention is premised on the general observation that a synergistic effect is elicited by administration of a CTL-inducing antigen formulation and an agent that antagonizes immunosuppressive factors. Compositions of the invention can include any effective agent that neutralizes or down regulates the activity of an immunosuppressive factor. As identified in the application as originally filed, numerous immunosuppressive factors are known, such as interleukin 10, prostaglandin (PGE2), immunosuppressive acidic protein (IAP), and lipocortin-1 (LC1) (see page 7, lines 10-17). Contrary to the assertion of the examiner, antagonists of immunosuppressive factors are also known in the art, including SC-51089 analogs, which inhibit PGE2 (*see* Hallinan et al. (1996) *J Med Chem* 39:609-613, copy enclosed) and anti-IL10 antibodies (*see e.g.*, Levy et al. (1994) *J Clin Invest* 93:424-428, copy enclosed). Based on the knowledge in the art and availability of such antagonists, a skilled artisan could readily select an antagonist of an immunosuppressive factor for practice of the invention.

Based on the foregoing arguments, applicants respectfully request withdrawal of the rejection of claims 23, 25-26, and 32 under § 112, first paragraph as allegedly non-enabling.

Rejection of Claims Under 35 U.S.C. § 102(b)

Claims 23-25 and 27 are rejected under 35 U.S.C. § 102(b) as being anticipated by Wojtowicz-Praga et al. (1996) *J Immunol* 19(3):169-175 (Wojtowicz-Praga). The examiner

states that Wojtowicz-Praga teaches a method of treating cancer via administering to a subject a TGFβ antagonist and an adjuvant (IL-2) capable of inducing cytotoxic T lymphocyte responses. In particular, the examiner states that Wojtowicz-Praga teaches immunostimulating properties of IL-2, including support of T cell growth, augmentation of the cytolytic activity of NK cells, stimulation of the proliferation and antibody production of B lymphocytes, enhancement of monocyte cytotoxicity (page 170, col. 2). Official action, page 7. This rejection is respectfully traversed.

Claim 23 is amended to clarify that an adjuvant composition, *i.e.* adjuvant in combination with an antigen, is administered such that the T cell response is antigen-specific cytotoxic T cell cytolysis. Support for the amendment can be found in the application as originally filed, including at page 6, lines 10-12, wherein it is described that the disclosed combination therapy enhances a CTL response against targeted antigen-expressing cells; at page 10, lines 7-9, wherein it is described that the CTL inducing composition is an antigen formulation; and in U.S. Patent No. 5,585,103, incorporated into the instant application by reference (*see* page 4, line 12), which describes antigen-specific cytotoxic T cell lysis of an antigen formulation useful in the present invention.

The present invention is patentably distinguished over Wojtowicz-Praga, which does not describe administration of an antigen nor antigen-specific cellular lysis by T cells. In addition, contrary to the suggestion of the examiner, the T cell lymphocyte activities described by Wojtowicz-Praga **do not** encompass activities of an adjuvant which induces antigen-specific cytotxic T cell cytolysis. Specifically, Wojtowicz-Praga describes T cell growth, which is a an antigen-independent response, and lytic activities of cells other than T cells, *i.e.*, NK cells (granular, non-T cell lymphocytes) and monocytes (macrophage precursors).

Based on the foregoing, it is clear that Wojtowicz-Praga lacks at least the element of inducing an antigen-specific CTL response, as in claim 23. Claims 24-25 and 27 ultimately depend from claim 23 and also include these elements. Thus, applicants request that the rejection of 23-25 and 27 under 35 U.S.C. § 102(b) be withdrawn.

Rejection of Claims Under 35 U.S.C. § 103(a)
Based on Wojtowicz-Praga, Arteaga, and Segarini

Claims 23-27 and 29 are also rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Wojtowicz-Praga in view of Arteaga et al. (1993) *J Clin Invest* 92:2569-

2576 (Arteaga) and further in view of PCT International Publication No. WO 94/09815 to Segarini et al. (Segarini). The examiner relies on Arteaga as teaching breast cancer therapies that employ anti-TGFβ antibodies, and on Segarini as teaching therapeutic methods involving subcutaneous, intravenous, intradermal, or intraperitoneal administration of soluble TGFβ fragments. In the view of the examiner, it would have been obvious to modify the method of Wojtowicz-Praga to include the teachings of Arteaga and Segarini to thereby arrive at the invention of claims 23-27 and 29. Official action, pages 8-10. This rejection is respectfully traversed.

As noted above in response to the rejection of claims under § 102(b), Wojtowicz-Praga lacks at least the element of administering an adjuvant composition which can induce an antigen-specific CTL response, as in claim 23. Claims 24-27 and 29 ultimately depend from claim 23 and also include these elements. Arteaga and Segarini do not cure the deficiency of Wojtowicz-Praga, as neither reference describes or suggests an antigen-specific CTL response. Given the deficiencies of the cited documents, applicants respectfully request that the rejection of claims 23-27 and 29 under § 103(a) based on Wojtowicz-Praga, Arteaga, and Segarini be withdrawn.

Rejection of Claims Under 35 U.S.C. § 103(a)
Based on Raychaudhuri, Hoefer, and Arteaga

Claims 32-33 are further rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,695,770 to Raychaudhuri et al. (Raychaudhuri) in view of Hoefer et al. (1995) *Cancer Immunol Immunother* 41:302-308 (Hoefer) or in view of Arteaga. The examiner relies on Raychaudhuri as teaching a method for the treatment of neoplastic or cancerous growths via administering a microfluidized antigen formulation, on Arteaga as teaching breast cancer therapies that employ anti-TGFβ antibodies, and on Hoefer as teaching a method for the treatment of cancer via down-regulation or neutralization of TGFβ activity. In the view of the examiner, it would have been obvious, at the time of the instant invention, to combine the antigen formulation of Raychaudhuri with a TGFβ antagonist, as taught by Hoefer or Arteaga, given that each composition has been used separately for cancer therapy. Official action, pages 10-12.

The Court of Appeals for the Federal Circuit has repeatedly held that secondary considerations such as unexpected results can effectively rebut a finding of *prima facie* obviousness. *See e.g., In re Geisler*, 116 F.3d 1465, 1469, 43 U.S.P.Q.2d 1362 (Fed. Cir.

1997) (quoting *In re Soni*, 54 F.3d 746, 750, 34 U.S.P.Q.2d 1684, 1687 (Fed. Cir. 1995). Thus, even assuming *arguendo* that a *prima facie* case of obviousness has been established, the unexpected and synergistic qualities of the presently claimed combination are sufficient to overcome the examiner's finding.

The application as originally filed discloses that administration of a microfluidized antigen formulation in combination with an antagonist of an immunosuppressive factor, shows greater-than-additive anti-tumor activity than either antigen formulation or immunosuppressive factor administered alone. *See* Example 2 and Figure 2B. The synergistic activity of the claimed combination therapy is not reasonably predicted by the single agent studies of Raychaudhuri, Arteaga, or Hoefer. These unexpected results establish the non-obviousness of the claimed combination therapy.

Based on the foregoing arguments, applicants respectfully request withdrawal of the rejection of claims 32-33 under § 103(a) as allegedly unpatentable over Raychaudhuri, in view of Arteaga or Hoefer.

Discussion of New Claims

New claims 38-43 are added. New claims read on the elected invention of methods for treating cancer and other neoplastic diseases.

Support for the new claims 38-43 is found in the application as originally filed, including at page 4, lines 1-6, wherein it is described that the therapeutic efficacy of a vaccine can be enhanced via administration of an antagonist of an immunosuppressive factor, which increases a cytotoxic T lymphocyte response; and at page 2, lines 4-12, wherein it is described that representative vaccines known in the art include live viral and bacterial vectors, non-replicating plasmid DNA, and proteins and peptides that have been conjugated to a lipophilic compound.

New claims 38-43 are believed to be patentably distinguished over and non-obvious over the cited documents, which do not describe induction or enhancement of an antigen-specific cytotoxic T lymphoctye response.

Conclusion

All claims rejections and objections having been addressed, it is respectfully submitted that the present application is in condition for allowance. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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